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### Therapeutic drug monitoring

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## Chapter

General discussion and  
future perspectives

The goal of this thesis was to optimize moxifloxacin (MFX) treatment for tuberculosis (TB) patients. We therefore studied individual body fluid drug concentrations and integrated pharmacokinetic (PK) data with microbiological susceptibility against *Mycobacterium tuberculosis* (MTB). Findings of this thesis support the need to consider dose adjustment in TB patients. In order to facilitate dose optimization, we developed supportive analytical tools for timely detection of inappropriate drug-exposure. Nevertheless, there are still some uncertainties in finding the optimal dose for MFX in individual TB patients.

### **The role of fluoroquinolones for tuberculosis**

In short, pharmacological treatment success is defined as kill of MTB. However, a sub-population of slow-replicating TB bacilli is difficult to eradicate. MTB has a complex genetic program to escape the impact of host immunity, drugs and hypoxia by switching into this latent or persistent phenotype (1). This sub-population is therefore also difficult-to-reach as these bacilli persist in the hypoxic regions of pulmonary lesions (2). Because of this drug-tolerant phenotype, a successful drug-regimen consists of six months of multiple drugs (3), including drugs that have efficacy for persisting MTB. Few drugs have activity on this phenotype; of the first-line drugs, pyrazinamide and especially rifampicin (RIF) have the best capacity to reach and kill this MTB population (2,4,5). If RIF cannot be used, because of a mutation in the *rpoB* gene rendering the organism virtually completely unsusceptible for the drug, 18-20 months for the traditional multidrug-resistant (MDR)-TB treatment are advised to ensure treatment success (6).

The emergence of drug-resistance –with ever increasing inhibitory concentrations for 2<sup>nd</sup> line drugs– is the biggest threat of today's TB burden (**Chapter 1**). In **Chapter 2A**, we have reviewed the literature on the PK and pharmacodynamics (PD), as well as on the influence of co-administered agents on the PK and PD, of 14 fluoroquinolones (FQs) for drug-resistant TB. MFX turned out to be the preferred FQ. Indeed, MFX has high bactericidal and sterilizing activity and an excellent penetration in the alveolar macrophages, the epithelial lining fluid and the cerebrospinal fluid (7). The later-generation FQs MFX, gatifloxacin (GFX) or levofloxacin (LFX) are core agents of the 18-20 month rifampicin-resistant (RR)/MDR-TB regimen that is currently recommended, although both MFX and GFX are also *in vitro* active against the non-replicating, anaerobic MTB bacilli (6,8) and therefore capable of shortening TB treatment. Also, a stable cure in BALB/c mice after 4 months of an anti-TB backbone of MFX and RIF instead of 6 months of isoniazid (INH) and RIF, and the early bactericidal activity (EBA) results of MFX and GFX fuelled hope to design a new short-course regimen (9-13). This pre-clinical data was the reason to investigate the sterilizing capacity of GFX and MFX for TB in 3 observational cohort studies (RR/MDR-TB) and 2 Phase III trials (drug-

susceptible (DS)-TB), respectively (14-18). In fact, a 9-12 month regimen based on GFX (or MFX) was introduced in the latest (2016) WHO guidelines for RR/MDR-TB, restricted to patients with no resistance against FQs and 2<sup>nd</sup> line injectables, and no previous treatment with 2<sup>nd</sup> line anti-TB agents (6). Given the subject of this thesis, it is important to note that in 2 cohorts the so-called 'Bangladesh regimen' for RR/MDR-TB consisted of a higher than standard dosage of GFX (14,16). The two Phase III trials on MFX for pulmonary DS-TB did not show the results that were hoped for; after a 4-month MFX-based regimen recurrence rates were remarkably higher than after standard 1<sup>st</sup> line 6-months treatment (17,18). In **Chapter 2B** of this thesis we evaluated the current role of MFX, GFX and LFX for TB, including these two key studies, and hypothesized that the TB patients receiving a FQ might have been under-dosed based on PK/PD and drug-drug interactions. Ideally, the right fixed dose is identified for the majority of patients, and prognostic factors for a low drug-exposure are clarified to select the minority of patients that might benefit from plasma drug concentration monitoring. In this context, it is important to mention that MFX is still used off-label for TB and that its potential to prolong QTc remains a concern.

### Prognostic markers of a low moxifloxacin exposure

In **Chapter 4A** and **4B**, we observed a highly variable MFX exposure in our TB patients. We have shown that rifampicin drug-drug interaction (RIF DDI), male gender, minimal inhibitory concentration (MIC)  $\geq 0.25$  mg/L, human immunodeficiency virus (HIV)-infection and the early phases of TB treatment are potential *perpetrators* of a too low MFX exposure (19,20). With the exception of a high MIC value, each of these markers appears to independently change the bioavailability, the volume of distribution and/or the clearance of MFX, potentially resulting in a clinically relevant reduction of MFX exposure (7,19,20).

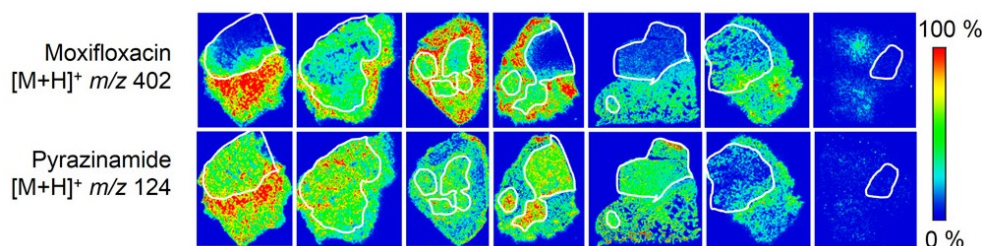
A global intensive concentration-monitoring program could help to further identify prognostic markers for a reduced anti-TB drug exposure, for example combinations of anti-TB and antiretroviral drugs to avoid in case of HIV co-infection. This program could also help to collect repeated concentration measurements in individual patients during the course of anti-TB drug therapy, thereby testing the hypothesis that TB disease severity influences the PK of MFX and other drugs (20). Perhaps, the recently (2017) initiated WHO task force on PK/PD of anti-TB drugs would be able to give direction on such a program. In addition, more knowledge on the PK mechanism behind prognostic markers might help clinicians to upgrade individual treatment regimens. Next to dose optimization, an upgrade might also be switching to another drug or temporarily switching to intravenous instead of oral administration. A cross-over PK study of oral and intravenous administration of MFX in TB patients, and

possibly of other anti-TB drugs, could have added value to investigate gender differences in absolute bioavailability (20).

### **Targets for adequate TB treatment with moxifloxacin**

Data on PK variability of anti-TB drugs is limited, but the problem of low drug-exposure has increasingly been recognized. A plasma drug-exposure failing to result in a drug concentration providing microbial inhibition is a threat for individual treatment success and therefore also, for TB elimination (21,22). However, targets for therapeutic drug monitoring (TDM) are generally understudied for anti-TB drugs. In BALB/c mice, the area under the concentration-time curve (AUC) divided by the MIC was proven to be the best parameter to predict *in vivo* efficacy of FQs against MTB (23). Apart from the inter-individual variability in drug-exposure, there is also a large variability in MICs for TB drugs. A genetic mutation results in different phenotypic susceptibility, but also genetic variations among 'wild type' organisms result in different MIC values (24). Due to occurrence of phenotypic single-drug tolerance against metabolically altered sub-populations of slow-replicating MTB bacilli, such organisms may survive causing failure or relapse (1). As mentioned earlier, MFX is active *in vitro* against the persisting bacilli in pulmonary or extra-pulmonary lesions, but also in these lesions or *niches*, the drug exposure has to be high enough for anti-microbial killing.

Given as mono-therapy, an  $AUC_{0-24h}/MIC$  ratio of  $\geq 100$  is suggested for bactericidal activity of FQs against MTB. The proposed target was based on the drug-exposure breakpoint associated with bactericidal activity of FQs against gram-negative bacteria, and its feasibility for bactericidal activity of MFX against MTB was confirmed in an *in vitro* PD model (19,25,26). Also, Monte Carlo simulations ( $n=10,000$ ) revealed that 59% of the TB patients are likely to reach the  $AUC_{0-24h}/MIC$  of 100 on 400mg MFX QD (26). In this context, it is important to note that this drug-exposure breakpoint was only identified to predict the bactericidal activity of MFX for TB bacilli in log-phase growth (26).



**Figure 1.** Ion maps of MFX (400mg QD) and of the well-known sterilizing drug pyrazinamide (1500mg QD) in lung lesions up to 24 hours post dosage by MALDI mass spectrometry. The white contour lines highlight the necrotic centre. The signal intensity is fixed for each drug and indicated by the rainbow colour scale bar. Adapted from Prideaux et al. 2015 (2) by permission from Springer Nature.

The penetration of MFX into the lesions tends to depend on the extent of cellularity (Figure 1) (2). If MFX is employed to shorten TB treatment, a higher plasma drug-exposure might be needed for sufficient drug-levels in more necrotic pulmonary lesions. In these TB patients selected for shorter treatment-regimens, a plasma  $AUC_{0-24h}/MIC$  of 100 might be too low. As mentioned earlier, there also might be a difference in drug-susceptibility between different sub-populations of MTB. It could therefore be at least questioned if a dose of 400mg MFX QD is high enough to shorten DS-TB treatment to four months only. We therefore propose the use of *in vitro* PD modelling to identify the optimal drug-exposure breakpoint associated with sterilizing effect (27). The earlier mentioned global PK data set on anti-TB drugs could then contribute to determine clinical dosages for subsets of patients.

Obviously, anti-TB drugs are never given alone, but are part of a multi-drug regimen. PD interactions (synergistic, antagonistic or additive) might influence the PD target of MFX. The combination of RIF and MFX has a greater suppressive effect on drug-resistant mutant selection of MTB in log-phase growth, but a smaller sterilizing effect, compared to the sum of the effect of the individual anti-TB drugs (28). For this drug-combination, individual drug-exposure targets for prevention of drug-resistant mutant selection of log-phase growth bacilli are probably lower than in case of mono-therapy (28). A MFX  $AUC_{0-24h}/MIC$  of 25 might well be optimal for an individual patient with adequate RIF drug-levels. Dose-escalation of MFX could still result in failure to result in a sterilizing effect, due to failure to eradicate persisters organisms. For precise dose adjustment of individual drugs as part of multi-drug regimens, it is thus needed to clarify PD interactions and their impact on individual PD targets to be used for TDM. Since patients have been reported with MTB resistant against almost all second-line drugs (29-31), development of new short-course drug-regimens based on drugs with a

sterilizing capacity, e.g. RIF or MFX, is needed, but perhaps less potent companion drugs could be used as boosters to suppress drug-resistance, if these drugs are used wisely based on PK/PD. This perspective is in line with the *in vitro* synergy between linezolid and the less potent drug clarithromycin for TB, and the boosting effect of low-dose ritonavir on exposure of a protease-inhibitor in the treatment of HIV (32,33).

### **Targets for a safe TB treatment with moxifloxacin**

A major concern for prolonged treatment is that adverse effects, like diarrhoea and vomiting, may result in a decreased compliance eventually resulting in drug resistance. We reported that a daily dose of 400mg MFX was well tolerated in 89 TB patients for a prolonged period, but there is also a strong indication that the MFX dose has to be escalated in subsets of patients (19,26). A major safety concern for dose-escalation of MFX is its potential to prolong the QT interval eventually resulting in a risk of Torsade de Pointes. In healthy volunteers (n=20), MFX significantly ( $p<0.05$ ) increased the QT interval at RR=400-1000ms, compared to placebo. In none of the healthy volunteers the QTc interval was  $>500\text{ms}$ , but a  $\Delta\text{QTc}$  of 63ms on 400mg MFX QD was observed in one subject, thereby exceeding the commonly used threshold for discontinuation of anti-arrhythmic drugs in clinical studies (34,35). In this study (34), a strong correlation ( $r=0.72$ ,  $p<0.001$ ) was found between the drug-levels in plasma and  $\Delta\text{QT}$  interval relative to placebo. We observed a highly variable MFX exposure in our TB patients (19,20). However, the median  $\text{AUC}_{0-24\text{h}}$  of  $25\text{ mg}\cdot\text{h/L}$  on 400mg QD in our TB patients is much lower than the geometric mean  $\text{AUC}_{0-\infty}$  of  $42\text{ mg}\cdot\text{h/L}$  on 400mg QD in the healthy volunteers studied (19,34). Therefore, the QT prolongation risk might be lower in the majority of TB patients. Concerning safety of high-dose MFX in TB patients, clinical data is limited, but no increase of serious adverse events on 800mg QD has been observed in our TB clinic, nor has been published to date (36,37). Recently, a concentration-effect analysis based on a thorough QT study was published for Chinese healthy volunteers (n=24) on 400mg MFX, to investigate, among others, the impact of ethnicity on the relationship of MFX concentration with QT interval prolongation (38). Perhaps, such analyses based on published MFX PK data of thorough QT studies, for which MFX is used as positive control, could also help to test the hypothesis that stepwise dose-optimization in TB patients is safe along with ECG monitoring around the expected peak-level.

### Therapeutic drug monitoring for every patient?

As earlier stated in this thesis, a PK/PD approach could be of added value in finding the best fixed FQ dose for the majority of DS- or RR/MDR-TB patients, and to guide the best MFX dose in individual TB patients at risk for a too low exposure. The American Thoracic Society adopted TDM in their TB treatment guidelines (2016) and the WHO has recently (2017) setup a task force on PK/PD of anti-TB drugs. As PK/PD finally gets the attention it deserved, PK and PD diagnostics are needed.

In **Chapter 3** of this thesis, we developed a LC-MS/MS method to determine MFX in plasma, plasma ultra-filtrate and cerebrospinal fluid (39), and in **Chapter 5** we have shown that two well-timed limited samples, 4 and 14 hours post dose, combined with population PK modelling, provide high-quality information on MFX plasma exposure and will overcome the need of extensive monitoring (40). However, in TB endemic countries devoid of this PK technology, less sophisticated techniques and simple sampling methods are needed to be able to quickly stepwise adjust to an effective and safe dose. We therefore also developed a Thin Layer Chromatography (TLC) method, using non-invasive oral fluid sampling (**Chapter 6**). To the best of our knowledge, this semi-quantitative method was the first technically validated. This technical validation is essential as the inter-observer error in visual read-out may be a potential flaw with major impact on clinical decision-making. Our observations provide evidence to support personalized dosing, but this low-tech test has to be evaluated in a larger sample of patients (41). Return of investment may be high as inadequately treated patients feed the TB epidemic. International organisations, like the Foundation for Innovative New Diagnostics (FIND), are needed for creation of awareness, on-site implementation and on-site evaluation of rapid TDM diagnostics for key anti-TB drugs, analogous to rapid diagnostics to detect drug-resistance against the same drugs. The number of samples needed for TDM could be limited and the sampling time-points could be optimized by developing more (practically applicable) limited sampling strategies for specific patient groups based on a larger population PK data set.



## **Conclusion**

In conclusion, if the PK variability of MFX is confirmed in a preferably larger PK data set, this could have several clinical implications. Further selection of patients at risk for a too low drug-exposure should be needed to safeguard the use of this key anti-TB drug. Standard dosages should be identified for subsets of patients based on established PK/PD targets. TDM diagnostics for individual dose titration in patients at risk for a too low drug-exposure should be implemented and evaluated.

## References

1. Boon C. and Dick T. 2012. How *Mycobacterium tuberculosis* goes to sleep: the dormancy survival regulator DosR a decade later. *Future Microbiol.* 7(4):513-8.
2. Prideaux B., Via L.E., Zimmerman M.D., Eum S., Sarathy J., O'Brien P., Chen C., Kaya F., Weiner D.M., Chen P.Y., Song T., Lee M., Shim T.S., Cho J.S., Kim W., Cho S.N., Olivier K.N., Barry C.E. 3<sup>rd</sup>, and Dartois V. 2015. The association between sterilizing activity and drug distribution into tuberculosis lesions. *Nat Med.* 21(10):1223-7.
3. World Health Organization (WHO) (ed.). 2017. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update). World Health Organization, Geneva, Switzerland.
4. Sarathy J.P., Via L.E., Weiner D., Blanc L., Boshoff H., Eugenin E.A., Barry C.E. 3<sup>rd</sup>, and Dartois V.A. 2017. Extreme drug tolerance of *Mycobacterium tuberculosis* in caseum. *Antimicrob Agents Chemother.* pii: AAC.02266-17.
5. Cano-Muniz S., Anthony R., Niemann S., and Alffenaar J.C. 2017. New approaches and therapeutic options for *Mycobacterium tuberculosis* in a dormant state. *Clin Microbiol Rev.* 31(1). pii: e00060-17.
6. World Health Organization (WHO) (ed.). 2016. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. World Health Organization, Geneva, Switzerland.
7. Pranger A.D., Alffenaar J.W., and Aarnoutse R.E. 2011. Fluoroquinolones, the cornerstone of treatment of drug-resistant tuberculosis: a pharmacokinetic and pharmacodynamic approach. *Curr Pharm Des.* 17(27):2900-30.
8. Lakshminarayana S.B., Huat T.B., Ho P.C., Manjunatha U.H., Dartois V., Dick T., and Rao S.P. 2015. Comprehensive physiochemical, pharmacokinetic and activity profiling of anti-TB agents. *J Antimicrob. Chemother.* 70(3):857-67.
9. Nuermberger E.L., Yoshimatsu T., Tyagi S., Williams K., Rosenthal I., O'Brien R.J., Vernon A.A., Chaisson R.E., Bishai W.R., and Grosset J.H. 2004. Moxifloxacin-containing regimen of reduced duration produce a stable cure in murine tuberculosis. *Am J Respir Crit Care Med.* 170(10):1131-4.
10. Dorman S.E., Johnson J.L., Goldberg S., Muzanye G., Padayatchi N., Bozeman L., Heilig C.M., Bernardo J., Choudhri S., Grosset J.H., Guy E., Guyadeen P., Leus M.C., Maltas G., Menzies D., Nuermberger E.L., Villarino M., Vernon A., and Chaisson R.E.; Tuberculosis Trials Consortium. 2009. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med.* 180(3):273-80.
11. Burman W.J., Goldberg S., Johnson J.L., Muzanye G., Engle M., Mosher A.W., Choudhri S., Daley C.L., Munsiff S.S., Zhao Z., Vernon A., and Chaisson R.E. 2006. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med.* 174(3):331-8.
12. Conde M.B., Efron A., Loredó C., De Souza G.R., Graca N.P., Cezar M.C., Ram M., Chaudhary M.A., Bishai W.R., Kritski A.L., and Chaisson R.E. 2009. Moxifloxacin versus

- ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet*. 373(9670):1183-9.
13. Rustomjee R., Lienhardt C., Kanyok T., Davies G.R., Levin J., Mthiyane T., Reddy C., Sturm A.W., Sirgel F.A., Allen J., Coleman D.J., Fourie B., and Mitchison D.A.; Gatifloxacin for TB (OFLOTUB) study team. 2008. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 12(2):128-38.
  14. Van Deun A., Maug A.K., Salim M.A., Das P.K., Sarker M.R., Daru P., and Rieder H.L. 2010. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 182(5):684-92.
  15. Kuaban C., Noeske J., Rieder H.L., Ait-Khaled N., Abena Foe J.L., and Trebucq A. 2015. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis*. 19(5):517-24.
  16. Piubello A., Harouna S.H., Souleymane M.B., Boukary I., Morou S., Daouda M., Hanki Y., and van Deun A. 2014. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis*. 18(10):1188-94.
  17. Gillespie S.H., Crook A.M., McHugh T.D., Mendel C.M., Meredith S.K., Murray S.R., Pappas F., Phillips P.P., Nunn A.J; REMoxTB Consortium. 2014. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 371(17):1577-87.
  18. Jindani A., Harrison T.S., Nunn A.J., Phillips P.P., Churchyard G.J., Charalambous S., Hatherill M., Geldenhuys H., McIlleron H.M., Zvada S.P., Mungofa S., Shah N.A., Zizhou S., Magweta L., Shepard J., Nyirenda S., van Dijk J.H., Clouting H.E., Coleman D., Bateson A.L., McHugh T.D., Butcher P.D., Mitchison D.A; RIFAQUIN Trial Team. 2014. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 371(17):1599-608.
  19. Pranger A.D., van Altena R., Aarnoutse R.E., van Soolingen D., Uges D.R., Kosterink J.G., van der Werf T.S., and Alffenaar J.W. 2011. Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J*. 38(4):888-94.
  20. Pranger A.D., van Altena R., Akkerman O.W., de Lange W.C.M., van Soolingen D., Touw D.J., Uges D.R.A., van der Werf T.S., Kosterink J.G.W., and Alffenaar J.W.C. 2018. Low moxifloxacin exposure in male tuberculosis patients and the need for monitoring in early stages of treatment. *To be submitted*.
  21. Srivastava S., Pasipanodya J.G., Meek C., Leff R., and Gumbo T. 2011. Multidrug-resistant tuberculosis not due to non-compliance but due to between-patient pharmacokinetic variability. *J Infect Dis*. 204(12):1951-9.
  22. Alffenaar J.W., Migliori G.B., and Gumbo T. 2017. Multidrug-resistant tuberculosis: pharmacokinetic and pharmacodynamics science. *Lancet Infect Dis*. 17(9):898.
  23. Shandil R.K., Jayaram R., Kaur P., Gaonkar S., Suresh B.L., Mahesh B.N., Jayashree R., Nandi V., Bharath S., and Balasubramanian V. 2007. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. *Antimicrob Agents Chemother*. 51(2):576-82.

24. De Steenwinkel J.E., ten Kate M.T., de Knecht G.J., Kremer K., Aarnoutse R.E., Boeree M.J., Verbrugh H.A., van Soolingen D., Bakker-Woudenberg I.A. 2012. Drug susceptibility of *Mycobacterium tuberculosis* Beijing genotype and association with MDR TB. *Emerg Infect Dis.* 18(4):660-3.
25. Nuermberger E., and Grosset J. 2004. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. *Eur J Clin Microbiol Infect Dis.* 23(4):243-55.
26. Gumbo T., Louie A., Deziel M.R., Parsons L.M., Salfinger M., and Drusano G.L. 2004. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modelling. *J Infect Dis.* 190(9):1642-51.
27. Van Rijn S.P., Srivastava S., Wessels M.A., van Soolingen D., Alffenaar J.C., and Gumbo T. 2017. Sterilizing effect of ertapenem-clavulanate in a hollow fiber model of tuberculosis and implications on clinical dosing. *Antimicrob Agents Chemother.* pii: AAC.02039-16.
28. Drusano G.L., Sqambati N., Eichas A., Brown D.L., Kulawy R., and Louie A. 2010. The combination of rifampin plus moxifloxacin is synergistic for suppression of resistance but antagonistic for cell kill of *Mycobacterium tuberculosis* as determined in a hollow-fiber infection model. *MBio.* 1(3). pii: e00139-10.
29. Migliori G.B., De Iaco G., Besozzi G., Centis R., and Cirillo D.M. 2007. First tuberculosis cases in Italy resistant to all tested drugs. *Eurosurveillance.* 12(5):E070517.1.
30. Velyati A.A., Masjedi M.R., Farnia P., Tabarsi P., Ghanavi J., Ziazarifi A.H., and Hoffner S.E. 2009. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest.* 136(2):420-5.
31. Udawadia Z.F., Amale R.A., Ajbani K.K., and Rodrigues C. 2012. Totally drug-resistant tuberculosis in India. *Clin. Infect. Dis.* 54(4):579-81.
32. Bolhuis M.S., van der Laan T., Kosterink J.G., van der Werf T.S., van Soolingen D., and Alffenaar J.W. 2014. In vitro synergy between linezolid and clarithromycin against *Mycobacterium tuberculosis*. *Eur Respir J.* 44(3):808-11.
33. Medicines Evaluation Board (MEB) (ed.). 2017. Summary of product characteristics. Lopinavir/ritonavir. Medicines Evaluation Board, Utrecht, The Netherlands.
34. Démolis J.L., Kubitz D., Tennezé L., and Funck-Brentano C. 2000. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther.* 68(6):658-66.
35. International Conference on Harmonisation (ICH) (ed.). 2005. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (E14). International Conference on Harmonisation, Geneva, Switzerland.
36. Ruslami R., Ganiem A.R., Dian S., Apriani L., Achmad T.H., van der Ven A.J., Borm G., Aarnoutse R.E., and van Crevel R. 2013. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label randomised controlled phase 2 trial. *Lancet Infect Dis.* 13(1):27-35.

37. Alffenaar J.W., van Altena R., Bokkerink H.J., Luijckx G.J., van Soolingen D., Aarnoutse R.E., and van der Werf T.S. 2009. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. *Clin Infect Dis.* 49(7):1080-2.
38. Xu F.Y., Huang J.H., He Y.C., Liang L.Y., Li L.J., Yang J., Yin F., Xu L., Zheng Q.S., and Wang K. 2017. Population pharmacokinetics of moxifloxacin and its concentration-QT interval relationship modelling in Chinese healthy volunteers. *Acta Pharmacol Sin.* 38(11):1580-1588.
39. Pranger A.D., Alffenaar J.W., Wessels A.M., Greijdanus B., and Uges D.R. 2010. Determination of moxifloxacin in human plasma, plasma ultrafiltrate and cerebrospinal fluid by a rapid and simple liquid chromatography-tandem mass spectrometry method. *J Anal Toxicol.* 34(3):135-41.
40. Pranger A.D., Kosterink J.G., van Altena R., Aarnoutse R.E., van der Werf T.S., Uges D.R., and Alffenaar J.W. 2011. Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with tuberculosis. *Ther Drug Monit.* 33(3):350-4.
41. Pranger A.D., van den Heuvel E.R., Greijdanus B., van Altena R., de Lange W.C.M., van der Werf T.S., Kosterink J.G.W., Uges D.R.A., and Alffenaar J.W. 2018. Thin-layer chromatography to support TDM of moxifloxacin in resource-limited settings. *To be submitted.*



